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METABOLIC SYNDROME DEVELOPMENT IN RELATION TO LOW BIRTH WEIGHT

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The metabolic syndromes are constellation of major risk factor for high fasting tri-aceylglycerols, obesity, low level of HDL cholesterol, higher fasting plasma insulin, hypertension and impaired glucose tolerance. A rat model of maternal diet was used to observe this relationship. This study investigated the metabolic syndrome development in relation to low birth weight. In this study 4 pairs of rats was used and was divided into 2 groups each consisting of 2 pairs as G1 normal and G2 was taken from animal lab of national institute of food science and technology. Control group was fed standard diet. Experimental group was fed 50% low diet as compared to control group during child bearing and lactation period. Offspring of rats was introduced solid diet and then reviewed at 20 day and 40 day of age respectively. The mother body weight and feed intake was measured daily. The overall mean body weight of mothers was significantly increased in control and decreased in experimental group. The control dam's offspring body weight significantly higher than experimental dam's offspring till weaning, however low birth weight offspring of rats show catch-up growth after weaning or 20 days. Serum glucose, cholesterol level of low birth weight offspring of rat's was higher than normal weight offspring.

Keywords: Metabolic syndrome, Low birth, Glucose, Cholesterol, HDL-Cholesterol

INTRODUCTION

In medical study metabolic programming and developmental origins of disease at maturity become an important area of research. It is evident that early life circumstances control fetus growth may alter the anatomy and function of organ of fetus that influence whole life programming of organisms. This process is characterized as early life programming. Nutrients and hormone are two components of this programming (Seckl, 2004).

The metabolic syndrome are constellation of major risk factor for high fasting tri aceylglycerols, low level of high-density lipoprotein cholesterol, obesity, elevated fasting plasma insulin, hypertension and impaired glucose tolerance. These factors tend to assemblage with each other and having same history (Reven and Lecture, 1988).

Low birth weight characterized as weight of new born less than 2500 g by WHO. Low birth weight can be associated with intrauterine growth restriction or immature birth. In late stage of pregnancy intrauterine stress is a cause of low birth weight. It is contrary to Low birth weight of prematurity. Development of disease at maturity has strongest correlation with low birth weight which is link with intrauterine growth retardation (Yiu*et al*., 1999).

LBW is also linked with gums disease (Moreu*et al*., 2005). Reactive air way disease, particularly if untreated results increase chances of mother's death rate during pregnancy, high blood pressure and protein in urine, premature birth and low birth weight baby (Dewyea *et al*., 2005). Previously, the natural fibre (wheat porridge) has been identified for its effect on lipid, body weight and serum glucose level (Sadaf *et al*., 2014).

Both clinical and epidemiological studies showed that before birth aspects contribute a major portion in the development of metabolic syndrome (Gluckman and Hanson, 2004). Epidemiological studies associate weight at the time of birth is a risking aspect in the development of non-insulin-dependent diabetes mellitus middle age (Osmond and Barker, 2000). Same interaction was discovered for other metabolic syndrome, including cardiac disease (Leeson, 2001; Jaquet, 2003).

Fowden *et al*.(2005) postulate a hypothesis which demonstrate that due to intrauterine nutrients stress there is change in the level of cortisol, glucocorticoid receptor of hypothalamic pituitary adrenal (HPA) axis and organ corticotropin-releasing hormone mRNA. These hormonal changes slow down fetus growth and development in response to reduced nutrient supply in general (total energy restriction, less blood flow to fetus through placenta) or specific (maternal protein or iron deficiency or hypoxia) to increase its chances for survival. Maternal stress during pregnancy change the programming of hypothalamic pituitary adrenal axis leads toward the metabolic disorders in later life demonstrates by a number of researches.

Total reduction in mother's food up to 50% in late pregnancy leads to the damage β-cell development. If this reduction is continued during lactation period it leads toward less β-cell mass and number permanently results diabetes (Garofano *et al*., 1998). Obesity, higher fasting glucose concentration and hypertension (HTN) are due to

further reduction in mother's diet up to 30% (Vickers *et al*., 2000).

LBW has association with onset of obesity at maturity proved by a large number of researches (Barker, 2004; Malee *et al*., 2002). Disrupt growth and function of fetus β- cell, result less secretion of insulin, a mechanism of insulin resistance in malnourished fetus (Blondeau *et al*., 2001).

Recent research show evidence that susceptibility for the development of HTN can be lay out by pre-birth aspects Fetus growth retardation and premature baby birth is due to fetus undernourishment (Johnson and Evans, 1987; Bernstein *et al*., 2002). There is increase chances for the onset of HTN and CVD in undernourished fetus because nutrients restriction alter the structure and function of fetus organs, it is proposed by both epidemiological and animal model research (Woods, 2000; Holemans *et al*., 2003).

Barker (1995) revealed that under nutrition during fetus development lead to intrauterine growth restriction (IUGR) due to which not only low birth weight occurs but it also reprogrammed the organ development. In human the nephrons number is determined in fetus and after the 36 gestation week no new nephrons being formed (Hinchliffe*et al*., 1991). In humans IUGR results lower number of glomeruli (Manalich*et al*., 2000) which result development of glomerular and at last systematic hypertension in later life according to the hyper filtration theory.

Due to prenatal exposure of glucocorticoids the sensitivity of arterial wall to angiotensin 2 increases and increases the chances of higher blood pressure in fetus (Lindsay *et al*., 1996).

The study was designed to assess the relationship between low birth weight and metabolic syndrome, and to compare the biochemical measurement of low birth weight and normal weight offspring of rats.

MATERIALS AND METHODS

Area of research: Virgin female Wistar rats (initial weight 150 to 260 g) were used for the study was housed individually and was maintain at 22°C on a 12 h light/12 h darkness cycle. They were mated and day 0 of gestation was taken as the day on which vaginal plugs will expel. The control group (n=2) were fed on diet according to their weight. The experimental group (n=2) were fed 50% less diet according to their body weight throughout pregnancy and lactation. Spontaneous delivery was taken place on day 22 of pregnancy. For simplicity the two groups of offspring are termed 'control' (C) and 'low diet' (led), however it is emphasized that only the mothers underwent dietary manipulation. All rats' offspring were fasted overnight prior to the study and body weight, different test and organ weight of offspring were measured after 20 and 40 day of age respectively. Total 4 Pairs of rats were used and further study was conducted on their off-springs. Group I: 2 pairs of rats (Control) andGroup II: 2 pairs of rats (Experimental). Feed intake of virgin female Wistar rats were measured daily. Body weight of rats weremeasured weekly throughout the pregnancy and after delivery offspring body weight were also measured weekly. Glucose concentration was estimated by GOD-PAP method as described by Thomas and Labor, 1992. Cholesterol level of collected sera was measured by liquid cholesterol CHOD–PAP method according to the guidelines of Kim *et al.* (2011). For liver soundness, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) were determined by auto analyzer using the relevant test kit with standard method (Atessahin*et al.,* 2004). The control and experimental group offspring organ weight were being measured. Data were analyzed by the analysis of variance techniques mean ± standard error was calculated. Means of treatment were compared by Duncan's new multiple range test (Steel *et al*., 1997).

RESULTS

Physical Parameters

Body weight (g): Mean of body weight was non-significantly increased in 3rd weeks of control and decreased in 1st week of experimental period as compared to control and experimental period (Fig. 1).

Feed intake (g): Feed intake was non-significantly increased in 3rd weeks of control and decreased in 1st week of experimental period as compared to control and experimental period (Fig. 2).

Off spring (weight): The comparison mean of off spring was significantly increased in 40 day of experimental and decreased in 1st day of experimental period as compared to control and experimental period (Fig. 3).

Organ Weight

Liver weight (g): Mean liver weight was significantly ($P<0.01$) increased in 40 day of experimental and decreased in 20 days of experimental period as compared to control and experimental period. On the contrary, the overall mean liver weight was significantly increased in experimental and decreased in control group. However, the overall mean liver weight was significantly decreased in 20 day and increased in 40 days in low birth weight (Table 1).

Kidney weight (g): Mean kidney weight was found non-significantly different in the experimental and control group. Whereas, the overall mean kidney weight was significantly ($P<0.01$) decreased in experimental and increased in control group and also overall mean kidney weight was significantly ($P<0.01$) decreased in 20 days and increased in 40 days in low birth weight (Table 1).

Pancreas weight (g): Mean pancreas weight was found non-significant in control and experimental group in metabolic syndrome development in relation to low birth weight of rats. Overall mean pancreas weight was significantly ($P<0.01$) decreased in experimental and increased in control group. However, the overall mean kidney weight was

Table 1: Mean±SE of different organ weights (liver, kidney, pancreas, lungs and heart) metabolic syndrome development in relation to low birth weight of rats

Organ Weight	Control			Experimental		
	20 day	40 day	Overall Means	20 day	40 day	Overall Means
Liver	0.98±0.04^{c}	3.33±0.11^{b}	2.15±0.36^{B}	0.72±0.01^{d}	4.45±0.24^{a}	2.59±0.57^{A}
Kidney	0.36±0.03	0.76±0.03	0.56±0.06^{A}	0.26±0.02	0.74±0.02	0.50±0.07^{B}
Pancreas	0.120±0.023	0.260±0.014	0.190±0.025^{A}	0.060±0.002	0.160±0.013	0.110±0.017^{B}
Lungs	0.390±0.022^{c}	0.730±0.058^{b}	0.560±0.059	0.230±0.016^{d}	0.840±0.025^{a}	0.540±0.094
Heart	0.240±0.013	0.530±0.115	0.380±0.071	0.160±0.006	0.430±0.011	0.300±0.041

Table 2: Mean±SE of serum glucose, cholesterol, ALT and AST of metabolic syndrome development in relation to low birth weight

Parameters	Control			Experimental		
	20 day	40 day	Overall Means	20 day	40 day	Overall Means
Glucose	117.50±3.60	124.83±6.92	121.17±3.88^{B}	179.00±3.22	205.00±1.69	192.00±4.29^{A}
Cholesterol	69.17±5.17^{d}	85.83±1.92^{c}	77.50±3.64^{B}	117.50±3.01b	181.67±1.73^{a}	149.58±9.81^{A}
ALT	41.33±1.73	43.17±1.49	42.25±1.12^{B}	81.00±1.53	87.83±2.81	84.42±1.84^{A}
Alkaline Phosphotase	181.00±2.19^{d}	278.83±3.61^{c}	229.92±14.89^{B}	797.67±3.91^{b}	1788.50±50.67^{a}	1293.08±151.33^{A}

Mean sharing similar letter in a row or in a column are statistically non-significant (P>0.05). Small letters represent comparison among interaction means and capital letters are used for overall mean.

significantly (P<0.01) decreased in 20 day and increased in 40 day in low birth weight (Table 1.

Lungs weight: Mean lungs weight was significantly (P<0.01) increased in 40 day of experiment and decreased in 20 days of experimental period as compared to control and experimental period. On the other hand, overall mean lungs weight was non-significantly increased in control and decreased in experiment. While, the overall mean lung weight was significantly (P<0.01) decreased in 20 days and increased in 40 days in low birth weight (Table 1).

Heart weight: Mean heart weight was significantly (P<0.01) increased in 40 days of control and decreased in 20 days of experimental period as compared to control and experimental period. Overall mean heart weight was non-significantly increased in control and decreased in experiment group. However, the overall mean heart weight was significantly (P<0.01) decreased in 20 days and increased in 40 days in low birth weight (Table 1).

Biochemical Parameters

Glucose (mg/dL): Serum glucose was found non-significantly different in control and experimental groups. While, overall mean serum glucose was significantly (P<0.01) increased in control and decreased in experimental group. However, the overall mean serum glucose was significantly decreased in 20 days and increased in 40 days in low birth weight (Table 2).

Cholesterol (mg/dL): Serum cholesterol was significantly increased in 40 days of experiment and decreased in 20 days of control period as compared to control and experimental period. But, the overall mean serum cholesterol was significantly increased in control and decreased in experiment. Conversely, the overall mean serum cholesterol was significantly decreased in 20 day and increased in 40 day in low birth weight (Table 2).

Alanine transaminase (ALT; U/L): The comparison mean of serum ALT was observed non-significantly different between days and experiments. On the other hand, the overall mean serum ALT was significantly decreased in control and increased in experiment. However, the overall mean serum ALT was significantly decreased in 20 days and increased in 40 days in low birth weight (Table 2).

Alkaline Phosphotase (AP; U/L): Serum AP was non-significantly different among the days and experimental periods. Overall mean serum AP was significantly decreased in control and increased in experiment. Whereas, the overall mean serum AP was significantly decreased in 20 days and increased in 40 days in low birth weight (Table 2).

DISCUSSION

The overall mean body weight was found significantly changed in 1st week (172.50±10.95) followed by 2nd week (201.83±14.61) and 3rd week (229.17±11.00). However, the overall mean body weight was significantly increased in control (227.44±8.83) and decreased in experimental group (174.89±8.51) in low birth weight. The overall mean feed intake was significantly found in 1st week (14.33±2.89) followed by 2nd week (16.50±3.05) and 3rd week (19.17±2.94). However, the overall mean feed intake was significantly increased in control (23.00±0.96) and decreased in experimental group (10.33±1.00) in low birth weight. In rats 50% reduction in feed during the pregnancy result abnormal development of beta cell. There is permanent reduction in β-cell if this feed reduction continuous during lactation (Garofano, *et al.,* 1997).

There is significantly reduction in weight of offspring whose mother is given 50% less diet throughout pregnancy and lactation period as compared to control rats till 21 days but after weaning low birth weight offspring show catch-up growth and low birth weight offspring have significantly high body weight as compared to control offspring. Our

result is consistent with studies that reveal there is less satiety, increased feed intake results high epithelial fat pad and BMI in offspring who born underweight due to catch-up growth than others who have normal weight at the time of birth (Ong and Dunger, 2002). The mechanism basis of this catch-up growth is increased level of IGF-I in low birth weight children between 0 to 2 years as compared to normal weight children (Dorner and Plagemann, 1994). Another

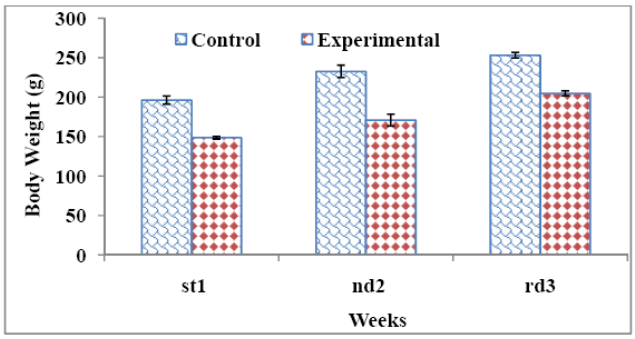

Figure 1: Mean±SE(g) of body weight of metabolic syndrome development in relation to low birth weight

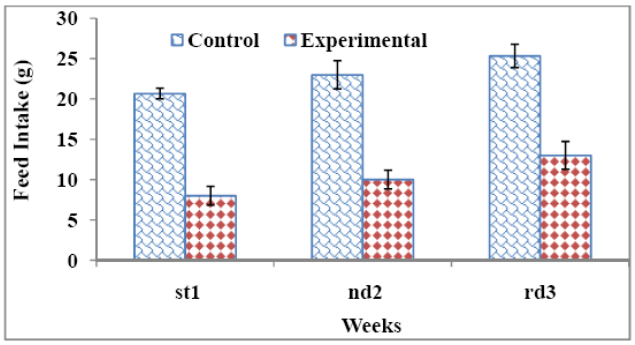

Figure 2: Mean±SE(g) of feed intake of metabolic syndrome development in relation to low birth weight

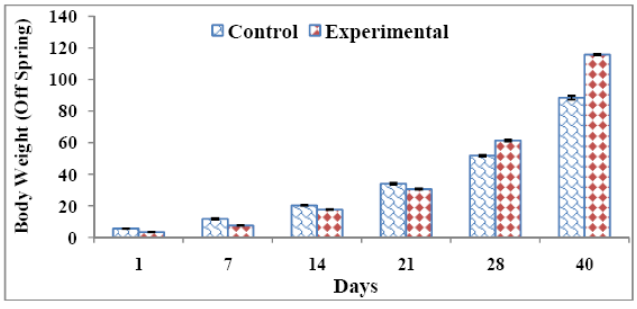

Figure 3: Mean±SE of variance of off spring of metabolic syndrome development in relation to low birth weight

reason of catch-up growth is increase expression of insulin receptor causes increased level of insulin and cortisol both these permanently change the programming of neuro-endocrine immune system. New born acquired obesity, Type 2 diabetes mellitus and other features of metabolic syndrome is due to mal functioning of hypothalamus (Doner*et al.,* 1987).

There is change in the structure and function of body such as organ weight in the intrauterine growth retarded offspring. Hales and Barker postulate a hypothesis in 2001 which is called Thrifty Phenotype Hypothesis. This hypothesis demonstrate that if mother is suffering from nutritional stress during pregnancy it change the metabolic structure of fetus to increase the chances of fetus survival by providing the energy to the vital organ like brain by compromise other organ health like pancreas. Such alteration during most significant period of fetus development permanently change the fetus metabolism structure in order to increase its chances for survival but later life when these individual expose to nutritional abundance at maturity these changes cause onset of metabolic disorders like Type 2 diabetes mellitus, hypertension, insulin resistance and obesity (Ravelli *et al*., 1998). The overall mean liver weight was significantly decreased in 20 days (0.85±0.04) and increased in 40 days (3.89±0.21) in low birth weight offspring as compared to control group offspring. Organ weight reduction such as liver, kidney, pancreas, lungs and heart is directly proportional to reduced body weight of offspring. After weaning organ weights are restored but their function are disturbed (Desai *et al.,* 1996). Desai *et al.* (1994, 1995) reveal that there is no recovery in the structure and function of organ although organ weights are restoring in later life but metabolism of liver is affected.

Serum glucose level of experimental group is non-significantly higher than control group at the age of 20 days but as the age increase serum glucose level of low birth weight offspring increased as compared to control group offspring. Research on different animals reveals that there is a higher chance of non-insulin dependent diabetes mellitus in low birth weight offspring (Rich-Edwards *et al.,* 1999; Lindsay *et al.,* 2000; Mi*et al.,* 2000). Research on animals proves that nutrition restriction before birth effect birth weight and metabolism of insulin and glucose in adult or later age (Arantes *et al.,* 2002; Holness, 1996; Hales *et al.,* 1996). There is increased risk of onset of non-insulin dependent diabetes mellitus in humans and decreased secretion of insulin and abnormal glucose metabolism in rats and sheep (Limesand *et al.,* 2006; Hale and Ozanne, 2003). There is less β- cell mass, decreased pancreatic insulin content and reduced response of insulin to glucose in intrauterine growth retarded young adult's offspring of rats (Simmons, 2008). Insulin secretion decreased and requirement of insulin increased in low birth weight adults. Another reason of increased insulin requirement of insulin in low birth weight offspring of rats is increased gluconeogenesis. There is increased process of gluconeogenesis in liver in low birth weight offspring result increased glucose level and resistant to insulin as compared to normal offspring (Vuguin *et al.,* 2004). There is increased quantity of enzyme play role in gluconeogenesis in low birth weight offspring of rat results change in liver glucose level and cause diabetes (Lane, 2002).

The comparison mean of serum cholesterol was significantly increased (181.67±1.73) in 40 days of experiment and decreased (69.17±5.17) in 20 days of control period as compared to control and experimental period. On the other hand, the overall mean serum cholesterol was significantly decreased in control (77.50±3.64) and increased in experiment (149.58±9.81). These results are consistent with the previous research. There is high concentration of serum cholesterol, low density lipoprotein in intrauterine growth retarded individuals proof by a study in United Kingdom (Barker, 1998; Barker *et al*., 1993; Martyn *et al.,* 1995). Increased low density lipoprotein concentration is recorded in low birth weight individual at adult or later age (Barker *et al*., 1993). Increased cholesterol is due to cranial redistribution of oxygenated blood away from the trunk to sustain brain metabolism—an adaptive response present in mammals. This impairs the growth of the liver and may underlie permanent abnormalities in the regulation of cholesterol and clotting factors (Rudolph, 1984).

The overall mean serum ALT was significantly decreased in control (42.25±1.12) and increased in experiment (84.42±1.84). However, the overall mean serum ALT was significantly decreased in 20 days (61.17±6.08) and increased in 40 days (65.50±6.90) in low birth weight. Elevation in ALT above 800U/L in low birth weight offspring is indicating disturbance in liver function (Schiele*et al.,* 1983).

The overall mean serum AP was significantly decreased in control (229.92±14.89) and increased in experiment (1293.08±151.33). However, the overall mean serum AP was significantly decreased in 20 days (489.33±92.99) and increased in 40 days (1033.67±228.88) in low birth weight.

CONCLUSION

Metabolic disease development in later life is influenced by poor nutrition during pregnancy, lactation and postnatal nutrition abundance. Nutritional stress during pregnancy cause intrauterine growth retardation results low birth weight offspring in rats. There is an association between low birth weight and metabolic syndrome development in young or later life. Low birth weight is associated with increased serum glucose, serum cholesterol and high level of A LT and AST in adult rat's offspring.

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